ARROWHEAD PHARMACEUTICALS

Fiscal 2021 Second Quarter Conference Call – Prepared Remarks

May 4, 2021

1:30 PM Pacific time

Operator

Ladies and gentlemen welcome to the Arrowhead Pharmaceuticals conference call. Throughout today's recorded presentation all participants will be in a listen-only mode. After the presentation, there will be an opportunity to ask questions. I will now hand the conference call over to Vincent Anzalone, Vice President of Investor Relations for Arrowhead. Please go-ahead Vince.

Vince Anzalone

Good afternoon everyone. Thank you for joining us today to discuss Arrowhead's results for its fiscal 2021 second quarter ended March 31, 2021.

With us today from management are president and CEO Dr. Christopher Anzalone, who will provide an overview of the quarter; Dr. Javier San Martin, our chief medical officer, who will provide an update on our pipeline; and Ken Myszkowski, our chief financial officer, who will give a review of the financials. In addition, James Hassard, our chief commercial officer, and Dr. James Hamilton, our senior vice president of Discovery & Translational Medicine, will be available during the Q&A session of today’s call.

Before we begin, I would like to remind you that comments made during today's call contain certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than statements of historical fact, including without limitation those with respect to Arrowhead's goals, plans, and strategies are forward-looking statements. These include statements regarding our expectations around the development, safety and efficacy of our drug candidates, projected cash runway, the receipt of future milestone and licensing payments, and expected future development and commercialization activities. These statements represent management's current expectations and are subject to numerous risks and uncertainties that could cause actual results to differ materially from those expressed in any forward-looking statements. For further details concerning these risks and uncertainties, please refer to our SEC filings, including our most recent annual report on Form 10-K and subsequent quarterly reports on Form 10-Q. Arrowhead disclaims any intent and undertakes no duty to update any of the forward-looking statements discussed on today's call.

With that said, I'd like to turn the call over to Christopher Anzalone, President and CEO of the Company. Chris?

Chris Anzalone

Thanks Vince. Good afternoon everyone and thank you for joining us today.

As we have discussed in the past, our driving focus has always been to bring our technology to patients who can benefit from it. This means treating all types of diseases, both common and rare, and getting to any part of the body. Put simply, it

means going to where disease is, from a population standpoint and a physiological and anatomical standpoint. As such, we are constantly working to expand the reach of our products to address various populations by scaling our production capabilities, improving administration convenience, and optimizing dosing schedule. We are also constantly striving to expand our proprietary TRiM™ platform to reach new cell types and address new disease areas without adequate treatment options. By the third quarter of this year, we expect to have clinical candidates targeting four distinct cell types, addressing high prevalence indications such as chronic HBV and cardiovascular disease, to rarer conditions such as cystic fibrosis and AAT liver disease. It was not that long ago that many thought RNAi may only be relevant to conditions with liver-expressed proteins, and even then only for rare diseases. We at Arrowhead have always been committed to reaching different diseases throughout the body and have devoted considerable resources and many years of innovation and effort to strive to make that a reality. We believe that we are now on the cusp of potentially gaining clinical validation and showing the world that RNAi can reach and silence gene targets in the lung, tumor, and skeletal muscle. We expect a data-rich next couple months, including:

- ARO-HSD data in NASH patients and those at risk of having NASH
- ARO-AAT data in patients with AAT liver disease
- ARO-ENAC data in healthy volunteers and a small number of CF patients
- ARO-HIF2 data in patients with renal cell carcinoma
- ARO-DUX4 data in animal models for FSHD

Three of these expected data readouts relate to three cell types that, to our knowledge, have not been successfully addressed by RNAi in humans. It is not big pharma with tens of thousands of employees and hundreds of billions in market value that may be on the cusp of a breakthrough in one of these areas; it is

Arrowhead with less than 300 employees and a market value of approximately $7bn that may be nearing a breakthrough in *all three*. Think about how that positions us for potential value creation over the near-, mid-, and long-term, and what it says about our ability to innovate and our potential to lead in this field. Our liver directed pipeline already has six candidates in clinical studies, with additional undisclosed programs in preclinical development. In addition, as you've seen over the last couple years, once we achieve clinical validation, each successive candidate in the same cell type builds on learnings from each program that went before it. We believe this provides a higher probability of success and lower risk profile than other modalities. We expect our pipeline to potentially double in size over the next few years. We also hope to access a new cell type every 18-24 months, so we believe our potential for growth will continue to expand dramatically. It's this leverage that gives us confidence about the future of our company, our rapidly expanding pipeline, and the patients we hope to serve.

We believe this represents the future for Arrowhead and for the RNAi field broadly. We're also making substantial progress on our current pipeline programs with the potential for key value drivers in the near-term. Let's talk about a few of these.

First, we announced some of the 12-month biopsy results from the 2002 open label study of ARO-AAT last week. We intend to present a fuller dataset at an upcoming medical meeting, pending abstract acceptance, but I want to provide some context. These results were incredibly exciting to us, our partners at Takeda, the investigators in the study, and to the patient community.

To review, the results demonstrated that ARO-AAT treatment led to a consistent and substantial reduction in intra-hepatic mutant Z-AAT protein, both monomer

and polymer; a consistent decrease in histological globule burden; improvements in fibrosis; and improvements in other relevant biomarkers of liver health. Specifically, after 48 weeks of treatment with ARO-AAT in cohort 2, the following results were observed:

- Four of the five patients achieved a 1 or greater stage improvement in Metavir fibrosis stage, with no worsening of fibrosis in the fifth patient
- All five patients demonstrated reductions in histological globule assessment scores; and,
- Total intra-hepatic Z-AAT decreased by 77-97%

After only 24 weeks of treatment, the following results were observed:

- Two of the four patients achieved a 1 or greater stage improvement in Metavir fibrosis stage, with no worsening of fibrosis in the other two patients
    - The two patients who improved fibrosis stages during treatment had cirrhosis at baseline
- All four patients demonstrated reductions in histological globule assessment scores; and,
- Total intra-hepatic Z-AAT decreased by 72-95%

I want to highlight a few important things about these results.

First, the results were remarkably consistent. We are seeing a 100% response rate in terms of deeply reducing Z-AAT expression, indicating that ARO-AAT is doing what it was designed to do in all patients that have been studied.

Second, we saw that as new Z-AAT protein is silenced, the liver has an amazing ability to rapidly heal. As I mentioned, 50% of patients who received only 6 months of treatment saw a regression in fibrosis, and this grew to 80% of patients when they received 12 months of treatment. This is faster and more dramatic than we expected for this disease, and I believe it is faster healing than has been shown for other liver diseases such as NASH and viral hepatitis.

The third important point is that even patients with cirrhosis, which is advanced late-stage liver disease, have the potential to heal rapidly. The 2 patients we studied who started the trial with cirrhosis, or F4 Metavir fibrosis stage, improved to F3 and F2 after only *6 months of treatment*. I believe that this type of rescue from cirrhosis has rarely been demonstrated in any liver disease this rapidly. Based on our extensive work in animal models, we believed that ARO-AAT could improve outcomes regardless of stage of disease. These are the first data in humans with late-stage disease that support that belief.

In addition, the safety assessments continue to be positive and consistent with previous reports. We have not had any discontinuations due to drug, no clinically meaningful changes in measures of lung function, and no patients have required augmentation therapy, other than those that entered the study already on regular augmentation therapy. ARO-AAT appears to be generally well-tolerated in those patients studied to date, which was our expectation and is consistent with our other liver-directed programs.

ARO-AAT is a great example of a smart target selection for an RNAi-based intervention. Alpha-1 liver disease is caused by accumulation of the mutant Z-AAT protein that cannot efficiently get out of hepatocytes. This leads to

aggregation of the protein into polymers that form globules, liver inflammation, and ultimately fibrosis. This cascade is well understood. It is a monogenic disease whose biology is crystal clear. What ARO-AAT seeks to do is cause the cascade to reverse by removing the insult. Our data indicate that the liver is a resilient organ with a strong ability to heal, and ARO-AAT appears to improve every step in the cascade.

These are encouraging results, and we believe they could help support our goal to seek a potential accelerated path to approval. We look forward to interacting with regulatory authorities later this year.

In addition to ARO-AAT, we've also made good progress on our cardiometabolic programs. These are ARO-APOC3 and ARO-ANG3, which are wholly owned, and Olpasiran, formerly called AMG 890, which was licensed to Amgen. On the latter program, Amgen recently disclosed that enrollment in a Phase 2 study in patients with elevated lipoprotein(a) is expected to be complete this quarter, with data expected in the first half of 2022.

For ARO-APOC3 and ARO-ANG3, we completed IND filings in the United States, which were reviewed by the FDA and are now active, and we intend to initiate four or more studies across the two programs. We will give more detail on the designs when each study gets up and running, but here are the patient populations that we are targeting:

For ARO-APOC3, which is focused on patients with hypertriglyceridemia, we intend to start three studies:

- A Phase 2b study in patients with triglycerides over 500 mg/dL

- A Phase 2b study in patients with triglycerides between 150-500 mg/dL; and,
- A Phase 3 study in patients with familial chylomicronemia syndrome, or FCS

For ARO-ANG3, which is focused on patients with mixed dyslipidemia characterized by elevated triglycerides and elevated LDL cholesterol, we intend to start a Phase 2b study.

For both programs, we are also exploring additional smaller studies to answer specific questions about the compounds, but the four just mentioned are the primary studies we are focused on initiating first.

Before I discuss expectations on timing of key near-term events across our pipeline, I want to highlight an announcement we made a few weeks ago. We announced ARO-DUX4 as Arrowhead's first muscle targeted candidate built on the TRIM™ platform. ARO-DUX4 is designed to target the gene that encodes human double homeobox 4 protein, or DUX4, as a potential treatment for patients with facioscapulohumeral muscular dystrophy, or FSHD.

FSHD is a genetic disease associated with the failure to maintain complete epigenetic suppression of DUX4 expression in muscle. This leads to overexpression of DUX4, which is myotoxic and can lead to muscle degeneration. There are currently no effective treatments specifically for FSHD. DUX4 fits perfectly with our strategy not only to bring RNAi outside the liver, but also to select gene targets that we believe are clear causes of specific diseases and for which there is strong biologic and genetic validation. We intend to file for

regulatory clearance in the third quarter of 2021 to begin clinical studies of ARO-DUX4.

Let's move on to our expectations for the near and mid-term. It's going to be a very busy time with several potentially important events and readouts. This is especially true for the next few months, so I'm going to focus on events planned for June and July. We expect to do the following in roughly this order:

1. Dose the first patients in the first ARO-APOC3 Phase 2b study, with a second Phase 2b and a Phase 3 study in patients with FCS planned for shortly after that
2. Dose the first patients in the ARO-ANG3 2001 Phase 2b study
3. Report initial interim results from the ARO-ENaC first-in-human study. This will likely include the Single Ascending Dose safety results in healthy volunteers, gene knockdown data in the cohort of healthy volunteers that received bronchial brushings and lavage, and data from the first cohort of patients with Cystic Fibrosis
4. Report full 12-month biopsy results from the 2002 open-label study of ARO-AAT
5. Report initial interim results from the ARO-HSD first-in-human study
6. Present preclinical data on ARO-DUX4 at the FSHD Society International Research Congress
7. Report initial interim results from the ARO-HIF2 first-in-human study
8. File a CTA for ARO-DUX4 and potentially host a KOL webinar to discuss the disease, the market opportunity, and the potential development path; and,
9. Announce additional programs in the pulmonary space that are already deep into preclinical development and in IND-enabling stage.

These are just the events that we expect over the next couple months. We clearly have a very full plate in the near-term, and we expect continued regular important catalysts going forward. We have been expanding in R&D to support this growing pipeline and are thrilled to see that we can still execute efficiently, even as a larger organization. Innovation, speed, precision, and capital efficiency have been hallmarks of the Arrowhead culture from the beginning and these principles will continue to be part of our DNA as a company.

With that overview, I'd now like to turn the call over to Dr. Javier San Martin. Javier?

Javier San Martin

Thank you, Chris, and good afternoon everyone.

Since we just reported topline results from the 12-month biopsy of the ARO-AAT 2002 open label study and we plan on reporting full data on the first 5 patients shortly, I want to talk about that program first. As Chris mentioned, the consistent fibrosis regression at these early timepoints was unexpected and very exciting. Importantly, we think they demonstrate the clear biological relationship between intra-hepatic Z-AAT and the downstream cascade of events that lead to liver inflammation and fibrosis. The relationship between Z-AAT and fibrosis is a key link. The idea is that substantial reduction in accumulated Z-AAT protein may allow the liver, even at the stage of cirrhosis, to reverse this cascade and ultimately heal and remodel itself.

So, what is next? If you recall, the original idea for the SEQUOIA study was an adaptive design Phase 2/3 study with a dose selection stage and then 2 years of

treatment at the selected dose in additional patients. Given the encouraging data we have seen in the 2002 open label study, we thought a potentially faster route to NDA would be to make SEQUOIA into a more traditional Phase 2 study, then discuss approvable endpoints with regulators in the context of all the data we will have generated. We are nearing completion of enrollment of the 36 patients in the SEQUOIA Phase 2 and expect to have 12-month paired biopsies for them next year. In addition, we expect to have data from the 16 patients in the 2002 open label study, which gives us approximately 50 patients with paired biopsies. We will also be able to compare data from multiple timepoints and with different dose levels. For an orphan disease, this is a substantial amount of data. We look forward to discussing the rich data set with regulators.

We feel very strongly that we will have a comprehensive picture of how ARO-AAT performs. I can't say that this will be enough to file an NDA, but we believe the data continue to support some form of accelerated path to approval. ARO-AAT is being co-developed with Takeda. We are still leading development and regulatory interactions at this time. The plan is to transfer the IND and give the lead to the team at Takeda, once the Phase 2 studies are complete.

As Chris mentioned earlier, we expect ARO-ENaC, ARO-HSD, and ARO-HIF2 to have initial interim data readouts over the next couple months. Since these are preliminary results from ongoing studies, we will likely provide highlights in a press release and then present a fuller data set at an appropriate medical meeting. Let's talk about what data might be included and which cohorts are available for each program.

I will start with ARO-ENaC, our inhaled RNAi therapeutic candidate designed to target the epithelial sodium channel to treat cystic fibrosis, or CF. CF is a rare

disease caused by a genetic mutation that leads to mucus buildup in the lungs. It is characterized by airway dehydration and reduced mucociliary transport. Patients with CF can have difficulty breathing and experience frequent and persistent lung infections.

The current strategy is to administer ARO-ENaC in what we call dose cycles. Each dose cycle is three consecutive days of receiving a nebulized dose of ARO-ENaC, or placebo. Repeat dose cycles occur three weeks later. So, for example, if a patient receives two dose cycles, they will receive a nebulized dose on day 1, 2, and 3, and then again on day 22, 23, and 24.

ARO-ENaC is in a Phase 1/2 dose-escalating study. We have administered ARO-ENaC in 16 normal healthy volunteers, who received a single dose cycle at four different dose levels, to assess safety and tolerability. We have also administered ARO-ENaC in an additional 12 normal healthy volunteers, who undergo bronchoscopy with bronchial brushings and bronchio-alveolar lavage or BAL, at baseline and at day 18 to evaluate ENaC knockdown in the lung. These subjects receive one dose cycle of 180 mg of ARO-ENaC or placebo.

The CF patient portion of the study includes three cohorts – two with six patients each and one with twelve patients. Patients in these cohorts receive two dose cycles and it is placebo controlled. The first cohort of six patients, four of which received ARO-ENaC at a dose of 40 mg and two received placebo, is complete and we are still in the blinded follow up stage. The second cohort will receive a dose of 65 mg and the third cohort will receive a dose of 180 mg.

We will be reporting interim results on the four SAD healthy volunteer cohorts, the one healthy volunteer bronchoscopy cohort, and the first cohort of CF patients.

What we will be watching most closely is safety and tolerability across the cohorts and the ENaC knockdown from the bronchoscopy cohort. For the CF patient cohort, we will also be measuring FEV1, however at this lowest dose and with only 4 patients on active drug, we do not expect to be able to detect changes in lung function. As we get to higher doses, longer exposure, larger sample sizes, and are able to select a more homogeneous patient population it is our hope that ENaC inhibition will lead to improvements in mucociliary clearance and lung function.

The next program with a planned readout over the coming months is ARO-HSD, our investigational candidate for the potential treatment of alcohol and nonalcohol related liver disease. We think the genetic data supporting HSD17B13 as a target for NASH and alcoholic liver disease is strong.

We are conducting a Phase 1/2 study in normal healthy volunteers as well as in patients with NASH or suspected NASH. We have completed the single dose portion of the study in healthy volunteers and have completed dosing in two of the four multiple-dose cohorts in patients with NASH or suspected NASH patients. Target engagement in patients, in the form of HSD17B13 mRNA and protein knockdown, will be assessed with liver biopsies. In this study the purpose of the biopsy is to obtain tissue to evaluate gene target knockdown. As the study is short in duration, we are not assessing changes in histology. This mechanism is not intended to reduce liver fat, so we don't expect to see any change in MRI-PDFF. We will be looking at other biomarkers of liver health to see if there are any early encouraging signs, but we are most focused on ARO-HSD's ability to reduce expression of its gene target at different doses. NASH has been a difficult area for drug developers, but HSD17B13 is a novel target and we believe there is very strong genetic validation. If we can show good knockdown and safety, we will have confidence in moving towards a Phase 2 study to assess efficacy.

The last program for which we expect to have a clinical readout in the near term is ARO-HIF2, which is designed to inhibit the production of HIF-2α to treat clear cell renal cell carcinoma or RCC. We are currently conducting a Phase 1b dose-finding clinical study in 3 cohorts with advanced clear cell RCC. The study is designed to evaluate the safety of ARO-HIF2, to determine the recommended Phase 2 dose, and to assess pharmacokinetics and preliminary efficacy, based on RECIST, and post-dose tumoral expression of HIF2-alpha and HIF associated genes.

We have completed dosing in two of the three cohorts and should be able to report on those two cohorts in the coming two months. We made a protocol amendment last quarter to add patients to the study. These are heavily pretreated patients with metastatic lesions in different locations, so biopsy collection is challenging. The new patients were added to give us a better chance of having tumor samples that can be processed, evaluated, and analyzed. We will be looking for data suggesting functional delivery to tumors as well as measurable levels of HIF2 knockdown.

I will now turn the call over to Ken Myszkowski, Arrowhead's Chief Financial Officer. Ken?

Ken Myszkowski

Thank you, Javier, and good afternoon everyone.

As we reported today, our net loss for the quarter ended March 31, 2021 was $26.8 million or $0.26 per share based on 103.9 million fully-diluted weighted average shares outstanding. This compares with net loss of $19.8 million, or $0.20 per

share based on 101.7 million fully-diluted weighted average shares outstanding, for the quarter ended March 31, 2020.

Revenue for the quarter ended March 31, 2021 was $32.8 million, compared to $23.5 million for the quarter ended March 31, 2020. Revenue in both periods relates to the recognition of a portion of the upfront payments and milestones received from our license and collaboration agreements with Janssen, and revenue in the current period also includes the recognition of a portion of the $300 million upfront payment due upon the signing of our collaboration agreement with Takeda. This payment was received in January. Revenue for the Takeda agreement will be recognized as we continue to work toward completing our performance obligations of managing clinical trials in process and certain manufacturing related services. The remaining $266 million of revenue associated with the Takeda collaboration is anticipated to be recognized over approximately 2 years. Our performance and revenue recognition under the Janssen agreements is substantially complete. Any additional milestones achieved with our collaboration partners would be additive to this projection.

Total operating expenses for the quarter ended March 31, 2021 were $61.0 million, compared to $45.8 million for the quarter ended March 31, 2020. This increase is primarily due to increased personnel costs and non-cash stock compensation in R&D as our headcount continues to grow. The increase is also due to increased candidate specific and discovery R&D costs.

Net cash provided by operating activities during the quarter ended March 31, 2021 was $263.9 million, compared with net cash used by operating activities of $27.6 million during the quarter ended March 31, 2020. The key driver of this change

was the upfront payment received from Takeda in January. We estimate our cash burn run rate to be $50 to $60 million per quarter.

Turning to our balance sheet, our cash and investments totaled $674.8 million at March 31, 2021, compared to $453.0 million at September 30, 2020. The increase in our cash and investments was primarily due to the upfront payment received from Takeda, offset by cash used for operating activities.

Our common shares outstanding at March 31, 2021, were 104.0 million.

With that brief overview, I will now turn the call back to Chris.

Chris Anzalone

Thanks Ken.

Clearly there is a lot of progress being made and our pipeline is becoming broader and more advanced. The upcoming data readouts are exciting on their own because they potentially represent progress towards new therapies for patients without adequate treatment options. These are people with serious diseases, and this is important to remember.

What is also exciting to us as a company is that these data readouts in new tissue types potentially represent clinical validation for our expanding TRiM™ platform. This is the future for Arrowhead and holds the promise of initiating our next phase of rapid pipeline growth and value creation.

Thanks again for joining us today. I would now like to open the call to your questions. Operator?

Operator